

Atty. Dkt. No. SALK2270-2
(088802-5203)

steroid hydroxylation are indicated. The standard nomenclature for P450 enzymes has been utilized. P450R is the single P450 oxidoreductase required for hydroxylation of steroids. UGT1A6 is a rat uridine diphosphate (UDP)-glucuronosyltransferase that conjugates glucuronic acid to hydroxylated steroids. –

Please delete the paragraph on page 13, line 24 through page 14, line 2, and replace it with the following paragraph:

-- **Figure 6B** presents a schematic comparison of conserved glucocorticoid-response elements found in human CYP3 genes. The region of human CYP3A4 (SEQ ID NO: 33) shown is necessary and sufficient for glucocorticoid and rifampicin induction of the full-length promoter. Corresponding regions of CYP3A5 (SEQ ID NO: 34) and CYP3A7 (SEQ ID NO: 35) are shown (Barwick et al., *Mol. Pharmacol.* 50:10-16, 1996). –

Please delete the paragraph on page 15, lines 18-26, and replace it with the following paragraph:

-- Figure 8C illustrates that the DR-3 element is essential for SXR-mediated activation of CYP3A2, and is interchangeable with the IR-6 element. The wild type (DR3/WT (SEQ ID NO:39), filled bars) or mutant forms (DR3/M1 (SEQ ID NO:42), open bars; DR3/M2 (SEQ ID NO:43), stippled bars; and DR3/IR6, hatched bars) of CYP3A23 cellular promoter reporters were transfected into primary rat hepatocytes in the presence of expression vector for SXR. The ligand treatment and data presentation are the same as in 8A. RIF, rifampicin; CTZ, clotrimazole. Note the disruptions of DR-3 element (DR3/M1, and DR3/M2) abrogate the activation of CYP3A23, and the replacement of DR-3 element with IR-6 element (DR3/IR3) rescue the responsiveness. --

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Please delete the paragraph on page 22, lines 10-15, and replace it with the following paragraph:

-- Thus, the terms "SXR receptor" and "SXR polypeptide" are interchangeable as used herein and are intended to include functional fragments of the invention SXR polypeptide(s). Such fragments include peptides having the DNA binding and/or the ligand binding properties of SXR, e.g. the DNA binding domain thereof (e.g. amino acid residues 41-107 as shown in SEQ ID NO:2), the ligand binding domain thereof (e.g., amino acid residues 141-434 as shown in SEQ ID NO:2). --

Please delete the paragraph on page 23, lines 11-20, and replace it with the following paragraph:

-- Examples of response elements suitable for use in practice of the invention methods can be selected from the following:

DR-3,4,5=AGGTCAN_nAGGTCA, wherein n is 3 (SEQ ID NO: 44), 4 (SEQ ID NO: 45), or 5 (SEQ ID NO: 46);

βDR-3,4,5=AGTTCAN_nTGAACT, wherein n is 3 (SEQ ID NO: 22), 4 (SEQ ID NO: 47) or 5 (SEQ ID NO: 48) and

IR-6 = TGAAC_nAGGTCA, wherein n is 6 (SEQ ID NO: 23), and the like.

Those of skill in the art will recognize that any combination of nucleotides can be used to make up the 3, 4, 5, or 6 nucleotide spacer between the repeated half sites (i.e., N_n in SEQ ID NOS: 44, 45, 46, 22, 47, 48 or 23). --

Please delete the paragraph on page 57, lines 24-27, and replace it with the following paragraph:

-- CYP3A oligonucleotides tested had the following sequences:

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CYP3A4, tagaataTGAACtcaaaggAGGTCagtgaagg (SEQ ID NO: 33);

CYP3A5, tagaataTGAACtcaaaggAGGTAagcaaagg (SEQ ID NO:34); and

CYP3A7, tagaataTTAACTcaatggAGGCagtgaagg (SEQ ID NO:35). --

Please delete the paragraph on page 60, lines 3-17, and replace it with the following paragraph:

-- The fact that SXR is necessary and sufficient to render the induction of both human CYP3A4 and rat CYP3A23 gene in rodent hepatocytes by RIF suggested that the host cellular environment, SXR/PXR herein, rather than the gene structure, dictates the patterns of inducibility of CYP3A genes. The above notion would predict: (1) The SXR/PXR response element is essential for the activation of CYP3A genes; and (2) The response elements of SXR and PXR are interchangeable. Therefore, mutagenesis analysis was performed on the promoter of the rat CYP3A23 gene to examine these predictions. In vitro electrophoretic mobility shift assays showed that both SXR:RXR and PXR:RXR heterodimers efficiently bind to the DR-3 elements (5'TGAACtcaTGAACt 3' (SEQ ID NO: 39)) in the CYP3A23 promoter (Blumberg et al., 1998). As shown in Figure 8C, mutation of both half sites (DR3/M1) or a single half site (DR3/M2) abolished the PXR and/or SXR-mediated activation by PCN, RIF, and CTZ; on the other hand, replacement of the wild type DR-3 element by an IR-6 element of the human CYP3A4 gene promoter (Blumberg et al., 1998, and Kliewer et al., 1998) successfully rescue the inducibility by PCN, RIF and CTZ. --

Please delete the paragraph n page 61, lines 8-20, and replace it with the following paragraph:

-- Genomic DNA was isolated as described before (Xie et al., 1999). The polymerase chain reaction (PCR) was used to screen the transgene positive mice. Two